TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: SANSYL007

U S APPLICATION NO. (If known, see 37 CFR 1.5): 10/069179

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/07917	08 August 2000	16 August 1999

TITLE OF INVENTION:
USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

APPLICANT(S) FOR DO/EO/US

ROSENZWEIG, Pierre

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application.
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An executed oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    Citation of References
    Information Disclosure Statement by Applicant (Form PTO-1449)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/069179	PCT/EP00/07917	SANSYL007

17. ☒ The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1. 492 (a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and international Search Report not prepared by the EPO or JPO.....$1040.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....$890.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ...$740.00

International preliminary examination fee (37 CFR 1.482)paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4).....$710.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfy provisions of PCT Article 33(1)-(4).....$100.000

			ENTER APPROPRIATE BASIC FEE AMOUNT =	$	**890.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	22 -20 =	2	x $18.00	$	**36.00**
Independent claims	2 - 3 =	0	x $84.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $280.00	$	
			TOTAL OF ABOVE CALCULATIONS =	$	**926.00**
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
			SUBTOTAL =	$	
Processing fee of **$130.00** for furnishing the English translation later than [ ]20[ ]30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$	
			TOTAL NATIONAL FEE =	$	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$	**926.00**
				Amount to be refunded:	$
				Charged	**$926.00**

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **19-0091** in the amount of **$ 926.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **19-0091**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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PATENT TRADEMARK OFFICE

SIGNATURE 2/15/02 DATE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Filing under 35 U.S.C. § 371
Corresponding to International
Application No.: **PCT/EP00/07917**

Applicants: **ROSENZWEIG, Pierre**

International Filing Date: **08 August 2000**

For: **USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY**

CERTIFICATE UNDER 37 C.F.R. 1.10

Express Mail Label Number: **EL676470487US**

Date of Deposit: February 15, 2002

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service on the date indicated above and is addressed to: Commissioner for Patents, Box PCT, Attn: EO/US, Washington, DC 20231.

Geraldine D. Sher
Signature

Commissioner for Patents
Box PCT
Attn: EO/US
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the specification:

At page 1, please replace the title with the following rewritten title:

--USE OF MONOAMINE OXIDASE INHIBITORS FOR THE TREATMENT OF OBESITY--

Please replace the abstract page immediately following the claims with the following rewritten abstract:

--ABSTRACT

The present invention relates to the use of reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B for the treatment of obesity.--

In the Claims:

Please amend claims 1-11, cancel claim 12, and add new claims 13-23 as follows before calculating the filing fee for the above-identified application.

Please amend claims 1-11 as follows:

1. (Amended) A method for the treatment of obesity which comprises administering to a patient in need of such treatment a reversible selective inhibitor of monoamine oxidase A, a reversible selective inhibitor of monoamine oxidase B or a reversible mixed inhibitor of monoamine oxidase A and B.

2. (Amended) A method according to claim 1 which comprises administering a reversible mixed inhibitor of monoamine oxidase A and B.

3. (Amended) A method according to claim 2 wherein the reversible mixed inhibitor of monoamine oxidase A and B is chosen from [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-(methoxymethyl-3-(6-cyclopropyl-methoxybenzofuran-3-yl)oxazolidin-2-one.

4. (Amended) A method according to claim 1 which comprises administering a reversible selective inhibitor of monoamine oxidase B.

5. (Amended) A method according to claim 4 wherein the reversible selective inhibitor of monoamine oxidase B is chosen among lazabemide, milacemide, caroxazone and IFO.

6. (Amended) A method according to claim 4 wherein the reversible selective inhibitor of monoamine oxidase B is (*S*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

7. (Amended) A method according to claim 1 which comprises administering a reversible selective inhibitor of monoamine oxidase A.

8. (Amended) A method according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is chosen from befloxatone, moclobemide, brofaromine, phenoxathine,

esuprone, befol, RS 8359, T794, KP9, E 2011, toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine.

9. (Amended) A method according to claim 8 wherein the reversible selective inhibitor of monoamine oxidase A is befloxatone.

10. (Amended) A method according to claim 9 wherein the dosage amount of befloxatone is from about 2.5 to 40 mg per day.

11. (Amended) A method according to claim 10 wherein the amount of befloxatome is from about 10 to 20 mg.

Please cancel claim 12.

Please add the following new claims:

13. (New) A method of decreasing body weight in a patient in need thereof which comprises administering to said patient an effective amount of a reversible selective inhibitor of monoamine oxidase A, a reversible selective inhibitor of monoamine oxidase B or a reversible mixed inhibitor of monoamine oxidase A and B.

14. (New) A method according to claim 13 which comprises administering a reversible mixed inhibitor of monoamine oxidase A and B.

15. (New) A method according to claim 14 wherein the reversible mixed inhibitor of monoamine oxidase A and B is chosen from [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-(methoxymethyl-3-(6-cyclopropyl-methoxybenzofuran-3-yl)oxazolidin-2-one.

16. (New) A method according to claim 13 which comprises administering a reversible selective inhibitor of monoamine oxidase B.

17. (New) A method according to claim 16 wherein the reversible selective inhibitor of monoamine oxidase B is chosen among lazabemide, milacemide, caroxazone and IFO.

18. (New) A method according to claim 16 wherein the reversible selective inhibitor of monoamine oxidase B is (*S*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

19. (New) A method according to claim 13 which comprises administering a reversible selective inhibitor of monoamine oxidase A.

20. (New) A method according to claim 19 wherein the reversible selective inhibitor of monoamine oxidase A is chosen from befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359, T794, KP9, E 2011, toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine.

21. (New) A method according to claim 20 wherein the reversible selective inhibitor of monoamine oxidase A is befloxatone.

22. (New) A method according to claim 21 wherein the dosage amount of befloxatone is from about 2.5 to 40 mg per day.

23. (New) A method according to claim 22 wherein the amount of befloxatome is from about 10 to 20 mg.

REMARKS

The title and abstract have been amended to more clearly reflect applicant's invention of a method of treatment.

Claims 1-11 have been amended to put them in appropriate U.S. method-of-treatment format. The method of treatment language appears in the specification at page 2, lines 19-22.

Claim 12 has been canceled herein without prejudice to the prosecution thereof in a continuing application.

New claims 13-23 are directed to a method of decreasing body weight and correspond in scope to the methods of claims 1-11. Activity of the reversible selective inhibitors of MAO-A, the reversible selective inhibitors of MAO-B and the reversible mixed inhibitors of MAO-A and MAO-B in decreasing body weight is found in the specification at page 2, lines 10-13.

Claims 1-11 and 13-23 are in the application as amended.

Attached hereto is a marked-up version of the changes made to the claims by the instant amendment. The marked-up version is entitled "Version With Markings To Show Changes Made".

Respectfully submitted,

Date: 2/15/02

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Version With Markings to Show Changes Made

In the specification:

The title has been amended as follows:

USE OF MONOAMINE OXIDASE INHIBITORS [FOR THE MANUFACTURE OF DRUGS INTENDED] FOR THE TREATMENT OF OBESITY

The abstract page has been amended as follows:

[USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY]

[SANOFI-SYNTHELABO]

[ABSTRACT:] **ABSTRACT**

The present invention relates to the use of reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B [in the manufacture of drugs intended] for the treatment of obesity.

In the Claims:

Claims 1-11 have been amended as follows:

1. (Amended) [Use of] A method for the treatment of obesity which comprises administering to a patient in need of such treatment a reversible selective inhibitor of monoamine oxidase A, a reversible selective inhibitor of monoamine oxidase B or a reversible mixed inhibitor of monoamine oxidase A and B [for the manufacture of drugs intended for the treatment of obesity].

2. (Amended) [Use of] A method according to claim 1 which comprises administering a reversible mixed inhibitor of monoamine oxidase A and B [according to claim 1].

3. (Amended) ~~The use~~ A method according to claim 2 wherein the reversible mixed inhibitor of monoamine oxidase A and B is chosen ~~among~~ from [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-(methoxymethyl-3-(6-cyclopropyl-methoxybenzofuran-3-yl)oxazolidin-2-one.

4. (Amended) [Use of] A method according to claim 1 which comprises administering a reversible selective inhibitor of monoamine oxidase B [according to claim 1].

5. (Amended) [The use] A method according to claim 4 wherein the reversible selective inhibitor of monoamine oxidase B is chosen among lazabemide, milacemide, caroxazone and IFO.

6. (Amended) ~~The use~~ A method according to claim 4 wherein the reversible selective inhibitor of monoamine oxidase B is (*S*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

7. (Amended) [Use of] A method according to claim 1 which comprises administering a reversible selective inhibitor of monoamine oxidase A [according to claim 1].

8. (Amended) [The use] A method according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is chosen [among] from befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359 [(Sankyo)], T794 [(Tanabe)], KP9 [(Krenitsky, USA)], E 2011 [(Eisei)], toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine.

9. (Amended) [The use] A method according to claim [7] 8 wherein the reversible selective inhibitor of monoamine oxidase A is befloxatone.

10. (Amended) [The use] A method according to claim 9 wherein the dosage amount of befloxatone is from about 2.5 to 40 mg per day.

11. (Amended) [The use] A method according to claim 10 wherein the amount of befloxatone [to be administered] is from about 10 to 20 mg.

Claim 12 has been canceled.

Claims 13-23 have been added.

USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

The present invention relates to the use of monoamine oxidase inhibitors in the manufacture of drugs intended for the treatment of obesity.

Obesity is a major health problem in western societies and its prevalence is increasing. As described in Cheryl P. Kordik and Allen B. Reitz, *J. Med. Chem.* (1999), **42**(2), 181-201, reviewing the various known strategies to treat obesity, obesity is a "chronic condition characterized by overabundance of adipose tissue" which "correlates with risks such as high blood pressure, coronary heart disease, diabetes, altered steroid metabolism, gallstones and certain forms of cancer".

Obesity is a multifactorial disease and its treatment requires multidisciplinary approaches. The treatment includes diet, exercise, behavior change, pharmacotherapy, and surgery. In the medical treatment of obesity, different approaches may be considered. Drugs may decrease energy intake (central or peripheral action), decrease energy storage, increase energy expenditure, or have a combination of different actions. A few compounds are currently available in some countries. These include sibutramine (a serotonin and norepinephrine reuptake inhibitor) and orlistat (a pancreatic lipase inhibitor).

Disorders linked to disturbances of eating behavior include bulimia nervosa and anorexia nervosa. Bulimia nervosa is characterized by compulsive overeating binges followed by inappropriate compensatory behaviors such as vomiting, fasting, excessive exercise, and misuse of diuretics or laxatives to maintain a desired weight. This eating behavior is associated with comorbid psychopathology, and can result in serious medical complications (e.g., dental erosion, esophagitis, gastrointestinal irritation, electrolyte imbalances).

The treatment of bulimia nervosa differs from the treatment of common forms of obesity. It may include cognitive-behavioral therapy, group therapy, family therapy, individual psychotherapy, and pharmacotherapy (e.g., antidepressants). Since bulimia nervosa is associated with marked alteration in monoaminergic systems (Benedetti M.S. et al.: "monamine oxidase: from physiologicology to the design and clinical application of reversible inhibitors", *Advances in drug research* (1992), **23**, 65-125), a number of monoamine oxidase inhibitors have been tried in bulimia nervosa as reported in Liebowitz M.R. et al.: "reversible and irreversible

monamine oxidase inhibitors in other psychiatric disorders", *Acta Psychiatrica Scandinavica supplementum* (1990), **360**, 29-34; Kennedy S.H. et al.: "is there a role for selective monoamine oxidase inhibitor therapy in bulimia nervosa ? A placebo-controlled trial of brofaromine", *Journal of clinical psychopharmacology* (1993), **13**(6), 415-22; Priest R.G. et al.: "reversible and selective inhibitors of monoamine oxidase A in mental and other disorders", *Acta Psychatrica Scandinavica* (1995), **91**, Suppl. 386, 40-43; Wittal M.C. et al.: "Boulimia nervosa: A meta-analysis of phsychosocial and pharmacological treatments", *Behaviour therapy* (1999), **30**, 117-135.

It has now been found that reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monoamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B have activity in decreasing body weight of obese patients. They may act by decreasing energy intake and/or increasing energy expenditure.

Accordingly, the present invention relates to the use of reversible selective inhibitors of MAO-A, reversible selective inhibitors of MAO-B or reversible mixed inhibitors of MAO-A and MAO-B for the manufacture of drugs intended for the treatment of obesity.

The invention therefore further relates to a method of treating obesity by administering to a patient in need of such treatment a therapeutically effective amount of a reversible selective inhibitor of MAO-A, a reversible selective inhibitor of MAO-B or a reversible mixed inhibitor of MAO-A and MAO-B.

In fact, candidates for treatment may be men and women suffering from obesity or overweight.

Among reversible MAO-A inhibitors, befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359 (Sankyo), T794 (Tanabe), KP 9 (Krenitsky, USA), E 2011 (Eisei), toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine may be cited.

These compounds are known and their preparation are described in the art.

Among reversible selective inhibitors of MAO-B, lazabemide, milacemide, caroxazone and IFO may be cited.

Among reversible selective inhibitors of MAO-A, reversible selective inhibitors of MAO-B or reversible mixed inhibitors of MAO-A and MAO-B the following compounds may also be cited:

- compounds disclosed in patent application EP 699680, i.e. 3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one derivatives and particularly [3(*S*),3a(*S*)]-3-methoxymethyl-7-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one and [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one,

- compounds disclosed in patent application WO 96/38444, i.e. oxazolidin-2-one derivatives and particularly (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one,

- compounds disclosed in patent application WO 97/13768, i.e. oxazolidin-2-one derivatives and particularly (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one.

Befloxatone or 3-[4-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)phenyl]5(*R*)-methoxymethyl-2-oxazolidinone, which is known for its antidepressive and mild anxiolytic activity is particularly prefered as reversible MAO-A inhibitor. It is a reversible monamine oxidase inhibitor with both a very high affinity for the A isoform (MAO-A) and great selectivity versus the B isoform (MAO-B), which does not affect reuptake of noradrenaline (NA), serotonine (5-HT) or dopamine (DA).

Its chemical synthesis is described in EP 424244.

As reversible MAO-B inhibitor (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one is preferred.

As reversible mixed inhibitor of MAO-A and MAO-B [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one are preferred.

The active substance according to the invention can be administred to patients in a variety of pharmaceutical forms well-known in the art and particularly in the form of compositions formulated for administration by the oral, injectable, transdermal or rectal route.

For oral administration, said compositions can take the form of tablets, dragees or capsules prepared by the conventional techniques using known carriers and excipients, such as binding agents, fillers, lubricants and desintegration agents; they can also be in form of solutions, syrups or suspensions.

For administration by the injectable route, the compositions according to the invention may be in the form of injectable solutions, suspensions or emulsions containing an acceptable oily or aqueous liquid carrier.

For transdermal administration, the composition can take the form of a patch wherein the drug can be encompassed in a gel, solution, ointment or cream.

For rectal administration, the compositions may be in the form of suppositories containing the conventional bases for suppositories.

The percentage of active compound in such compositions may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is determined by the clinician according to the mode of administration, the age and weight of the patient and the patients response. Unit dosage forms may be administered in a single dose or in multiple divided doses to provide the appropriate daily dosage.

The daily dosage for example of befloxatone can range from about 2.5 to 40 mg, preferably from about 10 to 20 mg.

The following examples relating to pharmacological data and a galenic formulation illustrate the present invention.

Example 1

FEEDING BEHAVIOUR IN FASTED RATS

Male Wistar rats (Iffa-Credo) were individually housed in polycarbonate cages (48x26.5x21.5 cm) in a temperature- and humidity-controlled animal colony room (20±2°C) with a 12-hour light dark cycle (7 a.m. - 7 p.m.). At least 1 week before the experiment, every animal was often handled and administered saline by oral route in order to avoid stress. Food and water were available ad libitum, and all testing was done in the home cage. Rats were fasted for 24 hour before testing and allowed free access to water. In the morning of the test day, rats were first assigned to either a treatment or a control group then weighed and administered drug or vehicle p.o. (10.30 a.m.) and returned to their home cage. Thirty minutes later, a measured quantity of food (RMM, Harlan Ibérica) was made available to the animals. The food intake is calculated every hour until 6 hours after the drug

administration. (WO95/11894, Gehlert et al., *J. Pharmacol. Exp. Ther.* (1998), **287**, 122-127).

Grams of food consumed by the treated animals every hour was compared to food consumed by the control animals using one-way analysis of variance with a Newman-Keuls' test.

Table

Effect of befloxatone on food consumption during light period (7 a.m.-7 p.m.) in fasted rats (24 hours). Recording and access to food 11 a.m.-2 p.m.

Group		Food intake (g)		
		0 - 1 hour	0 - 2 hours	0 - 3 hours
Control (vehicle p.o.)		7.56 ± 0.33	11.0 ± 1.33	11.84 ± 1.37
Befloxatone (3 mg/kg p.o.)		5.12 ± 0.78*	7.94 ± 1.20	10.86 ± 0.94

*p< 0.05 vs control (ANOVA test)

Example 2

FEEDING BEHAVIOUR IN FED RATS

Male Wistar rats (Iffa-Credo) were individually housed into a temperature- and humidity-controlled animal room (20±2°C) with a 12-hour light dark cycle (4.30 a.m. - 4.30 p.m.). in polycarbonate special cages with transducers connected to MacLab system. This enables to record the food consumption at every moment of day (light/dark phase). A measured quantity of food (RMM, Harlan Ibérica) is placed on the cage just before dark onset.

In order to avoid any kind of stress that could have an effect on their behaviour, every rat is administered saline and put in the cage at least 1 or 2 days before the test. The food consumption is recorded, without interruption, during these

days. Once the animal is used to the cage, the test compound or vehicle are administered, by oral route.

Grams of food consumed by the animals during the first 4 hours after drug administration was compared to food consumed by the control animals over the same period of time, using one-way analysis of variance with a Newman-Keuls' test.

Table

Effect of 7 days treatment with befloxatone (10 mg/kg/day, p.o.) on food consumption during dark period (4.30 p.m. - 4.30 a.m.) in fed male Wistar rats

Days of treatment	Food intake (g)	
	Control vehicle p.o. (n=7)	Befloxatone 10 mg/kg/day, p.o. (n=6)
1	3.98 ± 0.63	3.03 ± 0.40
2	5.91 ± 0.85	3.31 ± 1.00
3	7.95 ± 0.68	5.32 ± 0.69*
4	7.35 ± 0.57	6.12 ± 0.50
5	8.75 ± 0.76	6.10 ± 0.59*
6	9.69 ± 0.98	6.98 ± 0.61*
7	10.1 ± 0.74	6.95 ± 0.75*

*p< 0.05 vs control (ANOVA test)

These results show that in the model using **fasted rats**, befloxatone (3 mg/kg p.o.) inhibits food intake by about 25% during the first hour after administration of the drug, and in the model of **fed rats** with recording of food consumption in the dark, befloxatone (10 mg/kg p.o.), once a day for 7 days, inhibits as from the third day, food intake during the first four hours after drug administration.

Exemple 3

BODY WEIGHT GAIN STUDY IN OBESE ZUCKER RATS

Befloxatone was studied in obese (fa/fa) Zucker rats, a genetic animal model of obesity.

Experimental procedure

Animals

Genetically obese Zucker (fa/fa) male rats and lean (+/?) male littermates were purchased from IFFA CREDO (France).

One week before the start of the experiment, animals were individually housed in polycarbonate cages (45 x 30 x 20 cm), with food (A04 standard diet, UAR, France) and water *ad libitum*, in a room with controlled temperature (23°C ± 1°C), in a reversed light-dark cycle (lights off at 9 h 00, on at 21 h 00) and total refresh air (12-15 times per hour). Obese and lean rats were 13 weeks old when used and weighed 380-430 g and 280-330 g respectively.

Drug

Befloxatone was suspended in an aqueous solution with 0.5 % Tween 80, and administered orally in a volume of 5 ml/kg.

Protocol

- Animals were treated p.o., once daily (at 9 h 00) for 5 weeks.

Four groups of obese (fa/fa) rats were administered vehicle or befloxatone at the doses of 1, 3 and 10 mg/kg/day.

Two groups of lean rats were administered vehicle or befloxatone (10 mg/kg/day).

- Daily food intake and body weight were recorded (at 8 h 00).

Results

Results are expressed as mean ± SEM for each treatment group. A two-way

ANOVA with repeated measures on time factor was conducted on food intake and cumulative body weight gain across weeks of befloxatone administration.

In obese rats, befloxatone induced a decrease (but non significant) of food intake over the treatment period. In lean rats this effect was more pronounced as food intake was significantly decreased on weeks 1 and 4.

A 5-week chronic treatment with befloxatone induced a dose related reduction of body weight gain in obese rats. This effect was significant from the first week of treatment for the dose of 10 mg/kg/day. In lean rats befloxatone (10mg/kg/day) also induced a similar and significant reduction of body weight gain. At the end of the treatment, weight gain was reduced by 26% ($p<0.05$) and 24% ($p<0.01$) in obese and lean rats respectively.

Example 4

ORAL FORMULATION

Befloxatone	2.5 mg	0.125 kg
Maize starch	5 mg	0.250 kg
Lactose monohydrate	83 mg	4.150 kg
Povidone K29/32	5 mg	0.250 kg
Crospovidone	4 mg	0.200 kg
Magnesium stearate	0.5 %	0.025 kg
size 3 gelatine capsule		

The befloxatone and approximately 10% of the lactose (415 g), were premixed for 10 minutes using a Turbula mixer. The mixture was then transferred to a Diosna mixer-granulator. The remainder of the lactose, the maize starch, the povidone, and half the crospovidone were added and mixed for 3 minutes. A sufficient quantity of water was added (13%) and the mixture granulated for 3 minutes. The granulate was dried in a ventilated oven and calibrated at 0.63 mm. The rest of the crospovidone, plus the magnesium stearate was added to the resulting granulate, and the whole was mixed using a Turbula mixer for 10 minutes, and then filled into size 3 capsules to a unit mass of 100 mg.

Claims

1. Use of a reversible selective inhibitor of monoamine oxidase A, reversible selective inhibitor of monoamine oxidase B or a reversible mixed inhibitor of monoamine oxidase A and B for the manufacture of drugs intended for the treatment of obesity.

2. Use of a reversible mixed inhibitor of monoamine oxidase A and B according to claim 1.

3. The use according to claim 2 wherein the reversible mixed inhibitor of monoamine oxidase A and B is chosen among [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one.

4. Use of a reversible selective inhibitor of monoamine oxidase B according to claim 1.

5. The use according to claim 4 wherein the reversible selective monoamine oxidase B is chosen among lazabemide, milacemide, caroxazone and IFO.

6. The use according to claim 4 wherein the reversible selective monoamine oxidase B is (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

7. Use of a reversible selective inihibtor of monoamine oxidase A according to claim 1.

8. The use according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is chosen among befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359 (Sankyo), T794 (Tanabe), KP 9 (Krenitsky,

USA), E 2011 (Eisei), toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine.

9. The use according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is befloxatone.

10. The use according to claim 9 wherein the dosage amount of befloxatone is from about 2.5 to 40 mg per day.

11. The use according to claim 10 wherein the amount of befloxatone to be administered is from 10 to 20 mg.

12. The use according to any of claims 1 to 11 wherein the inhibitor of monoamine oxidase is intended for administration by the oral, injectable, transdermal or rectal route.

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(54) Title: USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

(57) Abstract: The present invention relates to the use of reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monoamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B in the manufacture of drugs intended for the treatment of obesity.

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

__X__ Original _____ Supplemental _____ Substitute

As a below-named inventor, I hereby declare that:

My residence, citizenship and mailing address are given below under my name.

I/We believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

the application for which

___ is attached hereto.

___ was filed on _____ as United States
Application Serial No. _____
and was amended on _____ (if applicable)

___ was filed on 8 August 2000 as PCT International
Application No. PCT/EP00/07917
and was amended on _____ (if applicable)

I/We have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I/We acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in Section 1.56 of Title 37 of the Code of Federal Regulations, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I/We hereby claim foreign priority benefit under Section 119 (a) - (d) of Title 35 of the United States Code of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States identified below and also identify below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States filed by me on the same subject matter and having a filing date before that of the application(s) from which priority is claimed:

			Priority Claimed	
Country	Number	Filing Date	Yes	No
EUROPE	99116026.8	16 August 1999	X	

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Application No.	Filing Date

I/We hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT international application(s) designating the United States identified below:

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I/We hereby appoint Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my/our attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

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I/We hereby declare that all statements made herein and in the above-identified application of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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